Towards Elucidating the Fanconi Anemia Network Through Genomic and Proteomic Approaches

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2015

CHAPTER 7

General discussion:
do Fanconi anemia proteins play a role
in the cell cycle machinery?

The well-established FA/BRCA pathway plays an important role in the repair of DNA (Kottemann and Smogorzewska 2013). Nonetheless the FA/BRCA proteins have roles, although less recognized, in many other cellular processes such as response to oxidative stress and transcription regulation (Kaddar and Carreau 2012). In this thesis in which the FA/BRCA network is explored and expanded via genomic approaches, a connection of FA proteins with the centrosome and cell division is becoming apparent, an idea also supported by other recent findings (Zou et al. 2013; Kim et al. 2013; Nalepa et al. 2013).

Firstly, we show in chapter 2 via a ranking approach tailored for FA proteins that the top 150 of human FA-like proteins is enriched for genes involved in the cell cycle, more specifically for genes encoding proteins located at centrosome and playing a role in the cell division process. Secondly, we demonstrate in chapter 4 that *FANCA* and *BRCA1* are coregulated at the mRNA level together with genes that play a role at the centrosome. Thirdly, we discover an unexpected link of FA proteins with a major microcephaly protein WDR62/MCPH2 (Bilgüvar et al. 2010; Nicholas et al. 2010; Yu et al. 2010) which we show to interact with CEP170 as described in chapter 6. Besides other functions, WDR62/MCPH2 and CEP170 are thought to have functions at the centrosome and cell division level. Together, it could be hypothesized that FA protein(s) have a role at a centrosome checkpoint and thereby control proper and/or type of cell division. This hypothesis will be discussed.

Before we discuss the possible role of FA proteins at the centrosome we firstly describe the structure and function of the centrosome and the role of the centrosome in cell division. Subsequently we discuss how FA proteins may function at the centrosome and how disruption of this function may impact on several clinical and/or cellular characteristics of FA.

1. Centrosome

The centrosome functions as microtubule-organizing center (MTOC), as regulator of cell cycle progression, and is involved in cilliogenesis (a cell compartment important for extracellular signals). The most prominent role of the centrosome occurs during mitosis, in which the cell duplicates into two identical cells. During mitosis, the centrosome orchestrates the segregation of the chromosomes, positions the mitotic spindle for proper cell division, and duplicates itself (Pihan 2013; Paridaen et al. 2013).

Architecturally the centrosome has a fascinating structure: it consists of two centrioles positioned orthogonal, and each centriole consists of nine parallel microtubule triplets shaped around a cartwheel assembly in a cylindrical structure (Figure 1A). One centriole is always older than the other, since a new centriole

duplicates from the existing centriole (Figure 1B). The older centriole ("mother") additionally generates on the end of the centriole distal and subdistal appendages (outgrowth), opposite (distal) to which it attaches to the younger centriole (proximal; Figure 1A). The distal and subdistal appendages are needed for the connecting to the plasma membrane where it initiates ciliogenesis, the formation of a sensory organelle (Paridaen et al. 2013). Furthermore the mature centrosome is surrounded by a cloud of proteins called pericentriolar material (PCM). Multiple structural and regulatory proteins are located to specific areas within the centriole and PCM (for more details on centrosome structure, see (Pihan 2013)).

During the cell cycle the centrosome duplicates at the G1/S phase of the cell cycle, the two centrioles subsequently uncouple and are hold together through linker fibers during centriole elongation. In the process of centrosome duplication, the original younger (daughter) centriole grows distal and subdistal appendages and becomes a "mother centriole". When both chromosomes are matured, they separate at the G2/M (prophase) phase of the cell cycle, and move to opposite sides of the cell. When the cell has divides each cell has again one centrosome (Figure 1C) (Pihan 2013).

2. Cell division – symmetrical and asymmetrical

Cell division, in which one cell divides into two cells, is a process needed for growth. Division can result in two identical cells (symmetric cell division; SCD) or in two distinct cells (asymmetric cell division; ACD; Figure 2A). Symmetrical and asymmetrical cell division is used by cells during development and tissue homeostasis, such as by stem and neuronal cells. A tight balance is maintained between self-renewal and differentiating cells which is important to prevent tumorigenesis (overproliferation) or tissue degeneration (cell depletion) (Cheng et al. 2008; Izumi and Kaneko 2012).

The centrosome has been suggested to be involved in asymmetric cell division (Yamashita et al. 2007; Rebollo et al. 2007; Rusan and Peifer 2007; Cheng et al. 2008; Yamashita 2009; Wang et al. 2009). Several "age-related" characteristics of the centrosome play a role. The older centrioles with the distal and subdistal appendages have microtubule-anchoring activity, of which the oldest, the mother has the highest activity. On the other hand, the daughter centriole has greater motility than the mother centriole. Additionally, the pattern of centrosome inheritance (oldest mother centriole = mother centrosome versus new mother centriole = daughter centriole) in asymmetric cell division determines which capacity the cell receives, self-renewal or differentiation (Yamashita 2009; Izumi and Kaneko 2012). The exact mechanism of centrosome inheritance is still in debate (Figure 2B). In male germ line stem cells of the fruit fly the mother centrosome stays at the stem cell, and the daughter centrosome

migrates in the cell with differentiation capacity (Yamashita et al. 2007), on the other hand in the neuroblasts of the fruit fly the mother centrosome migrates to the cell with differentiation capacity and the daughter centrosome stays in the self-renewal cell (Conduit and Raff 2010; Januschke et al. 2011). Human neuroblastoma cells follow the mode of centrosome inheritance as described for fruit fly neuroblasts, daughter centrosome in self-renewal cell and mother centrosome in differentiating cell (Izumi and Kaneko 2012). In summary, mechanistically centrosome inheritance is not clear, and may be cell type specific; however it is clear that the centrosome is involved in cell division.

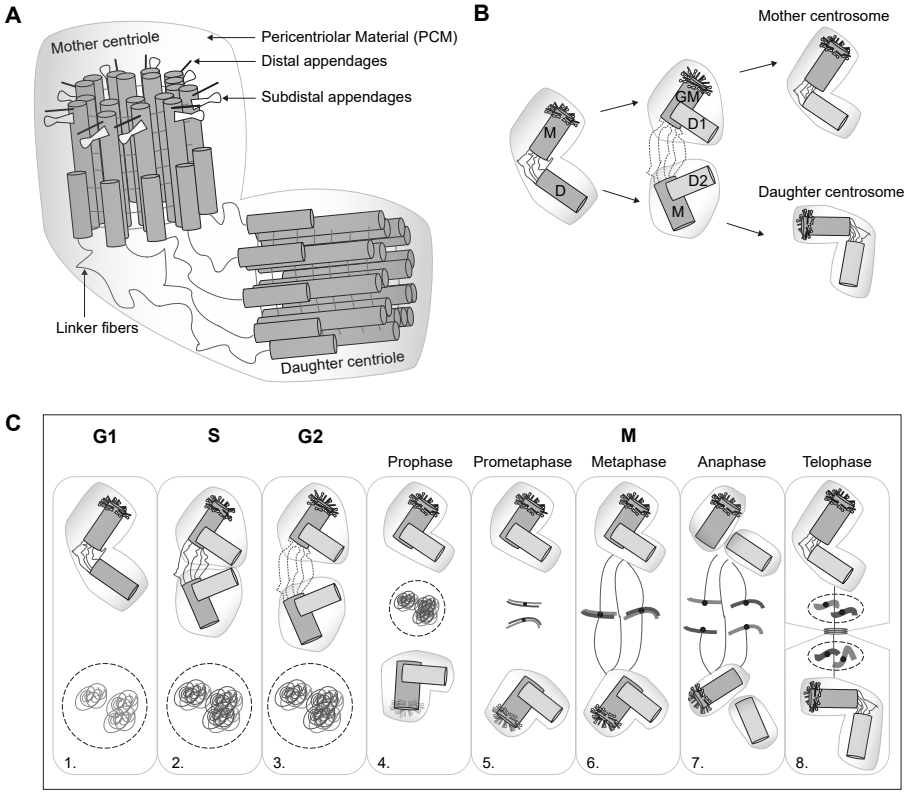

Figure 1. Centrosome.
(A) Schematic representation of a centrosome, consisting of two centrioles. (B) Centriole and centrosome age. A centrosome consists of two centrioles, one "mother" (M) and one "daughter"; after elongation (see also Figure 1C) each centriole is duplicated (D1 and D2), in which the initial "mother" centrioles turns to "grandmother centriole" (GM) and the initial "daughter" (D) centriole becomes a "mother centriole. After centrosome segregation one centrosome is called the "mother centrosome"; carrying the oldest centriole; and the other the "daughter centrosome" carrying the youngest centriole (C) Centrosome duplication during cell cycle 1) centriole disengagement 2) centrosome duplication 3) dissolution linker fibers and start centrosome separation 4-5) further centrosome separation and old daughter centriole changes into a mother centriole 6) bipolar spindle formation 7) centriole disengagement 8) centriole linker fiber formation. Figure A and C adapted from Pihan, 2013 (Pihan 2013).

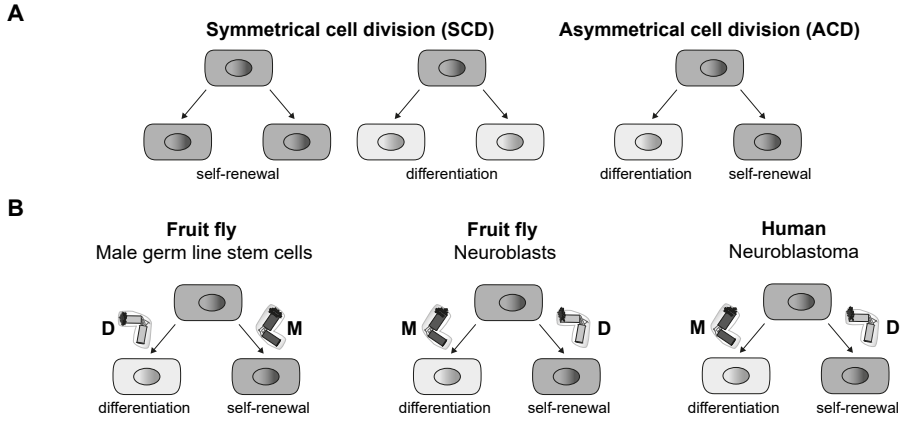

Figure 2. Cell division patterns and centrosome inheritance.
(A) Schematic representation of symmetric and asymmetric cell division. (B) Different modes of centrosome inheritance in asymmetric cell division. Abbreviations: D = daughter centrosome, M = mother centrosome.

3. Evidence role FA proteins at centrosome and cell division

So far the FA proteins have been linked to their role in DNA repair during cell division. However, evidence is accumulating that these may also play an important role at the centrosome level.

The first line of evidence that FA proteins might play a role at the centrosome and cell division was obtained from prioritization of the human proteome based on properties of known FA proteins. Ranking the entire proteome according to intrinsic FA protein properties, such as evolutionary conservation, combined with other FA-linked features as uncovered via publicly available biosemantics and other bioinformatics tools (chapter 2), resulted in a top 150 enriched not only for DNA repair genes, as was expected, but also for genes involved in the cell cycle. In more detail, the top 150 consist of genes that are located or have functions at the centrosome and genes involved in cell division (top 150; chapter 2 – table 3 and 8). Several proteins in the top 150 play a role in cell cycle checkpoints, e.g. CCNE1, CCNA1, CDC25B and CDC25C. Additionally, CEP250 (C-Nap1) is important for centriole-centriole cohesion during the interphase of the cell cycle (Kumar et al. 2013). In the same top 150 list, also two genes causative for MCPH-SCKL spectrum disorder were found (ATRIP and RBBP8). Encoded proteins of genes causing MCPH-SCKL are known for their functioning at the centrosome. Interestingly, KIF11 (Eg5), a protein important for centrosome separation (Mardin and Schiebel 2012), is also one of the proteins with FA protein properties. Since the prioritization was based on the 13 FA proteins known at the time, these findings overall suggest that centrosome and/or cell division proteins share several properties with FA/BRCA proteins.

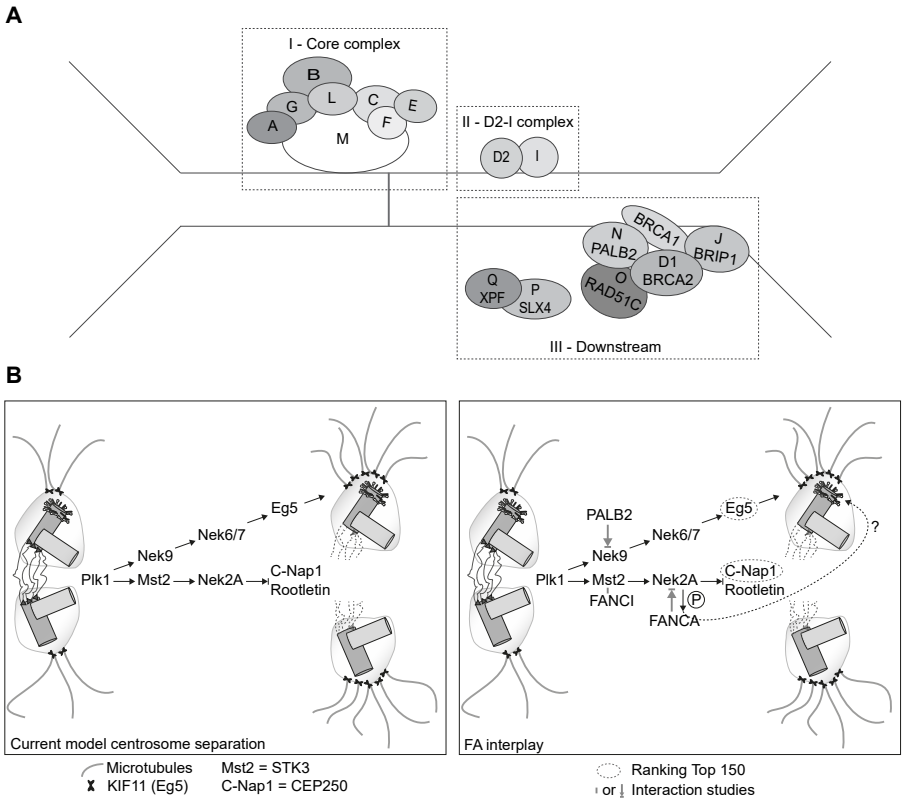

Figure 3. Canonical FA/BRCA pathway and centrosome separation model.
(A) Schematic representation of the canonical FA/BRCA pathway, dashed boxes illustrate the FA core complex (I); D2-I complex (II); and the downstream FA proteins (III). (B - Left panel) Schematic representation of current centrosome separation model, adapted from Mardin and Schiebel [21]. (B - Right panel) FA protein interplay in centrosome separation. PALB2 binds to CDK5RAP2 and NEK9 hypothetically preventing centrosome separation. Similar inhibition is accomplished via FANCI-STK3 (Mst2) interaction and FANCA-Nek2A interaction. Grey dashed circles indicate proteins highly resembling FA/BRCA proteins in general.

Secondly, while studying the FA/BRCA mRNA expression in relation to the cell cycle we found evidence for coregulation of *FANCA* and *BRCA1*. This was unforeseen since they function in different parts of the canonical FA/BRCA pathway (Figure 3A), whereas genes that are coregulated often function together. Strikingly, when mining public available gene expression databases the expression of *FANCA* and *BRCA1* is in line with several genes involved at the centrosome, including three genes causative for microcephaly-seckel (MCPH-SCKL) spectrum disorder (WDR62/MCPH2, CEP152/MCPH9/SCKL5, and CENPJ/MCPH6/SCKL4; chapter 4 – supplemental table 5). Intriguingly, centrosomal roles for both FANCA and BRCA1 have been reported (Kais et al. 2012; Zou et al. 2013; Kim et al. 2013); together with the centrosomal coregulation this suggest that FANCA (and BRCA1) have a bigger role at the centrosome level than former acknowledged.

Recently, a role of FANCA in maintenance of centrosomal integrity has been suggested based on the finding that FANCA localizes at the centrosome of mitotic cells and has a direct interaction with Nek2, a protein which activity controls dissolution of the linker fibers (Pihan 2013; Kim et al. 2013). Interestingly, Zou and collegues (Zou et al. 2013) demonstrated that FANCA mainly localizes specifically to the mother centriole during late G2 and mitosis. This last finding might be important to understand the pattern of centrosome inheritance in relation to asymmetric cell division. However, until now there is controversy if the mother centrosome remains in the cells with self-renewal potential or migrates into the cell with differentiation potential, and suggestive for cell type dependent events (Izumi and Kaneko 2012). Another possible function of the specific FANCA localization to the mother centriole lays in ciligonesis, since the cilia extends from the plasma membrane after docking of the mother centriole with the appendages to the plasma membrane (Nigg and Raff 2009; Avasthi and Marshall 2012). Interestingly, the cilia function in processes that are affected in FA patients, such as kidney development and links have been suggested with signaling, cell cycle progression, and cilia defects involved in cancer (Nigg and Raff 2009; Avasthi and Marshall 2012). It would be of interest to explore in which (or both) of the mechanisms (centrosome inheritance or ciliogenesis) FANCA is involved, and the consequences in case of a FANCA defect.

Thirdly, via co-immunoprecipitation studies combined with mass spectrometry to identify binding partners of FANCI and FANCN/PALB2 we unexpectedly identified several proteins that have functions at the centrosome [data not shown]. Until recently a puzzling finding, however, studies have shown now that both FANCI and FANCN/PALB2 can localize to the centrosome (Zou et al. 2013; Nalepa et al. 2013). The centrosomal localization of FANCI and FANCN/PALB2 suggest that the identified centrosomal binding partners are plausible. Interestingly, we identified both CEP170 and WDR62/MCPH2 as binding partners of FANCI [chapter 6; data not shown], and WDR62/MCPH2 as binding partner of FANCN/PALB2; in addition we confirmed CEP170 as a binding partner of WDR62/MCPH2 [chapter 6]. Furthermore, we identified several binding partners that are involved in centrosome cohesion and/or separation: CDK5RAP2/MCPH3/CEP215 (Graser et al. 2007; Barr et al. 2010), and NEK9 (Bertran et al. 2011; Mardin and Schiebel 2012) with FANCN/PALB2 [data not shown]; and STK3 (Mst2) with FANCI [data not shown]. Overall the interaction of FANCI and FANCN/PALB2 with centrosomal proteins suggest a yet to be identified molecular function at the centrosome.

Based on the data above and recent literature, a picture is emerging of a specific role for FA proteins (mirrored to their role in DNA repair – Figure 3A) in controlling the process of centrosome cohesion and/or separation which we will discuss according to

the current centrosome separation model (Figure 3B – left panel; (Mardin and Schiebel 2012)). In order to separate the two centrosomes at the G2/M cell cycle phase, two processes occur that both are regulated by PLK1. First, PLK1 activates a NEK9/6/7 signaling cascade that targets Eg5 (KIF11) to the centrosome, the centrosome separation driver. Secondly, PLK1 regulates the dissolution of the centrosomal linker via a binding-phospho-cascade which involves Mst2 (STK3), Nek2A, and C-Nap1 (CEP250). Interestingly, the first process includes NEK9 that we identified as a binding partner of FANCN/PALB2, suggesting a role for FANCN/PALB2 in controlling the cascade that drives centrosome separation (Figure 3B – right panel). Of note, it has been reported that FANCN/PALB2 (together with FANCD1/BRCA2) regulates G2 checkpoint maintenance, through retaining the AURORA A/BORA/PLK1 pathway in an inactive state (Menzel et al. 2011). Here we provide additional evidence for FANCN/PALB2 in regulating G2 checkpoint by regulating centrosome separation possibly via NEK9. In the second process of centrosome separation, the centrosomal linker dissolution, we have indications that FANCI interacts with Mst2 (STK3). In addition, FANCA has been reported to interact with NEK2A, and is required for centrosome integrity (Kim et al. 2013). This suggests that FANCI and FANCA have a role in the cascade that results in centrosomal linker dissolution. Furthermore, the two proteins with key functions in centrosome separation (Eg5/KIF11) and centrosomal linker dissolution (C-Nap1/ CEP250) share several properties with FA/BRCA proteins according to our ranking scheme, suggesting that they all are involved in a common network, e.g. centrosome separation and/or integrity.

In addition to the above discussed roles for FANCA, FANCI and FANCN/PALB2 in centrosome separation and/or integrity also FANCJ/BRIP1 and FANCM are involved. FANCJ/BRIP1 was reported to suppress centrosome amplification in normal situations, whereas upon stress (e.g. MMC) induces centrosome amplification, and suggested to work upstream of PLK1 (Zou et al. 2013). Intriguingly, FANCM degradation at the G2/M phase of the cell cycle is regulated by PLK1 (and β-TRCP) (Kee et al. 2009). In addition, FANCM depletion induces centrosome amplification (Collis et al. 2008). An interesting observation, since the FA/BRCA pathway is mostly active (in case of DNA damage) between mid/early S phase and late S phase/G2 (Deans and West 2011). Taken together the tightly regulated cell cycle and centrosome cycle, suggests synchronized function for FA proteins at the DNA repair level during mid/early S phase and late S phase/G2 followed by a centrosomal function from G2/M phase of the cell cycle onwards thereby assuring that DNA damage is repaired prior to centrosome separation and/or cell division.

4. FA phenotype, centrosomes, asymmetric and symmetric cell division

If FA proteins have a key role at maintaining and/or regulating centrosome cohesion and separation subsequently to their role in DNA repair this might provide possible explanations for specific FA hallmarks, including at the cellular level aneuploidy and asymmetric cell division, and at the organismal level, microcephaly and bone marrow failure.

A centrosomal role for FA proteins is plausible since FA deficient cells accumulate high numbers of centrosomes (Nalepa et al. 2013); the abnormal numbers of centrosome can contribute to aneuploidy – a hallmark of cancer (Vitre and Cleveland 2012). Interestingly, abnormal centrosome numbers are a common feature of tumors (Nigg 2002; Pihan 2013). The causes of centrosomal abnormalities in cancer are still debated, whether they are the result of intrinsic centrosome defects or are a secondary effect from other cellular processes (Pihan 2013). Nonetheless, several hypotheses concerning overduplication of centrosomes have been suggested, for example due to a defect in centrosome disengagement regulation (Shimada and Komatsu 2009). In relation to our hypothetical function of FA proteins in controlling centrosome cohesion and separation, this could explain the abnormal centrosomes seen in FA deficient cells. In FA deficient cells this control on centrosome cohesion is absent and consequently centrosomes might duplicate several times during one cell cycle, resulting in the abnormal centrosome numbers. In summary, the centrosomal defects in FA patients might be a primary event rather than a second event in the development of cancer in FA patients.

Intriguingly, centrosome abnormalities (increased centrosome numbers) in the developing of the brain causes microcephaly instead of tumors (Marthiens et al. 2013). About a fifth of FA patients are indicated with microcephaly (Shimamura and Alter 2010). Microcephaly is not a unique characteristic only for FA patients, but seen in several DNA repair disorders and is the key characteristic in the MCPH-SCKL spectrum [see General Introduction]. The overlap on the cellular level might be that the encoding proteins of genes underlying these diseases have all a role at the centrosome. In addition, in this thesis we demonstrate possible direct protein-protein interactions between proteins involved in MCPH-SCKL disorders, which provide a glimpse of the underlying complicated network. One general assumption to explain the smaller brain seen in MCPH-SCKL patients points to possible defects in spindle position (positioning centrosomes) during the neuronal stem cell expansion (symmetric cell division) leading to early depletion of the progenitor pool. Recent findings in mouse models suggest that the abnormal centrosome numbers lead to defects in cell division and consequently to an increase in apoptosis which also can result in a smaller brain (Marthiens et al. 2013).

Both microcephaly models involve the centrosome, and additional research is needed to demonstrate which model is more likely. Nonetheless both models demonstrate the link between centrosome and microcephaly and we suggest adding a link with FA proteins.

The last FA hallmark we want to discuss is the bone marrow failure in FA patients. The common hallmark of FA patients is aplastica anemia, a deficiency in all three blood cell types due to stem cells that are unable to generate the mature blood cells. In bone marrow failure syndromes such as FA it is believed that this is due to failure in DNA repair and consequently the accumulation of DNA damage in the hematopoietic stem cell (HSC) pool (Garaycoechea and Patel 2013). Normal hematopoietic stem cells can renew themselves and produce differentiating cells via asymmetric cell division and symmetric cell division (Morrison and Kimble 2006). The observation that FANCA specifically localizes to the mother centrosome together with the link of FANCI with CEP170 (subdistal = mother localization) and WDR62 (interaction CEP170) raises the possibility that FA proteins play a role in centrosome positioning. Centrosome positioning determines the type of cell division, asymmetric or symmetric. This raises the hypothesis, that some FA proteins might regulate the decision between asymmetric and symmetric cell division via centrosome positioning. In a FA background the cell division choice is disturbed and subsequently leads to the decline in HSC. The FA defect in cell division choice during development leads to failure in HSC expanding due to less efficient symmetric division; and after birth, the HSC pool is endangered due to incorrect switching between symmetric and asymmetric cell division. In addition, the previously discussed role for FA proteins in regulating centrosome cohesion and separation in combination with apoptosis can also be a possible mechanism for bone marrow failure. However, the role of asymmetric centrosome segregation, mode of centrosome inheritance, and cell fate still has to be resolved (Januschke and Näthke).

5. Concluding remarks

There is growing evidence that (several of) the FA proteins, in addition to their involvement in the FA/BRCA pathway of DNA repair, are also involved in the proper functioning of centrosomes during the cell cycle. This involvement might become manifest in diverse clinical features typically observed in FA patients, including bone marrow failure and microcephaly.

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